Tetrahedron Letters, Vol. 34, No. 45, pp. 7217-7220, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Direct Conversion of Esters to Secondary Amides using Tin(II) Reagents

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Abstract: We have developed two new procedures for the direct conversion of esters to secondary amides. In our first procedure, secondary amides can be prepared in 83-98% yield starting from glycol esters. Addition of $Sn[N(TMS)_2]_2$ and a primary amine to the glycol ester generates an intermediate tin(II) alkoxy amide, which delivers the amino group intramolecularly to give the amide. A second general procedure for the preparation of secondary amides starts with methyl esters. Treatment of methyl esters with a tin reagent derived from $Sn[N(TMS)_2]_2$, $Me_2NCH_2CH_2OH$, and a primary amine yields secondary amides in 87-98% yield.

We have found tin(II) amides of type $(TMS)_2N\text{-}Sn\text{-}NR_2$ (R=alkyl) to be a new and useful source of nucleophilic amines. Recently, we reported the utility of these reagents for the preparation of trans-N,N-dialkyl enamines from carbonyl compounds,[1] and for the direct conversion of esters to amides.[2] During the course of the latter work, we observed that tertiary amides were formed in higher yields than secondary amides under our general reaction conditions. In this paper, we provide new mechanistic information that rationalizes these results, and also report two improved procedures for the conversion of esters to secondary amides.

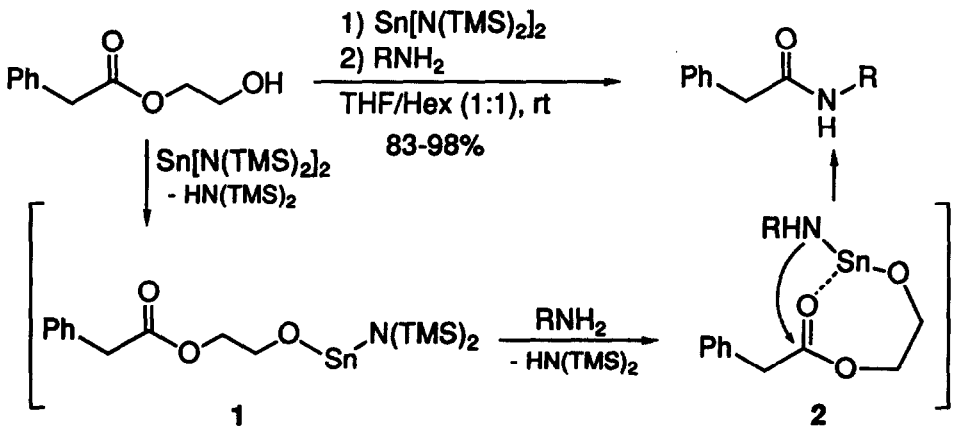
Previously, we showed that secondary amides were obtained in 63-67% yield when a primary amine was slowly added to a mixture of the ester and $Sn[N(TMS)_2]_2$.[3] This order of addition proved to be significant, as yields dropped dramatically when other permutations were tried. For example, reaction of methyl phenylacetate with benzylamine under our standard conditions gave the N-benzyl amide in 65% yield. When benzylamine was added to $Sn[N(TMS)_2]_2$, *followed by methyl phenylacetate*, however, the amide was obtained in only 5-22% yield.[4] We hypothesized that the low yield under these conditions resulted from formation of tin(II) amino cubanes.[5] These cubanes are apparently far less reactive than monomeric or dimeric tin(II) amides, and fail to react with esters.

Thus, any efforts to optimize the procedure for conversion of esters to secondary amides would have to minimize, or eliminate, the formation of tin(II) amino cubanes. It soon became apparent that modifications in the reaction solvent and/or the number of equivalents of reagents were not effective.[6] We then investigated a substrate controlled approach to minimize cubane formation. Previous work had shown that both α– and β-hydroxy esters could be converted to amides via an intramolecular reaction of intermediate tin(II) alkoxy amides. By

utilizing glycol esters instead of saturated alkyl esters, we reasoned that it would be possible to take advantage of an intramolecular pathway.

Indeed, this simple strategy proved quite effective. Treatment of the glycol ester of phenylacetic acid with $Sn[N(TMS)_2]_2$ and a primary aliphatic or aromatic amine yielded the corresponding amides in 83-98% yield (Scheme 1). We believe this reaction proceeds by an initial metathesis reaction between the hydroxyl group of the glycol ester and one of the silazane ligands on $Sn[N(TMS)_2]_2$ to form tin(II) alkoxy amide **1**. A second metathesis reaction between the remaining silazane ligand on **1** and the primary amine generates a new alkoxy amide **2**, which delivers the amine intramolecularly to the ester.

Scheme I



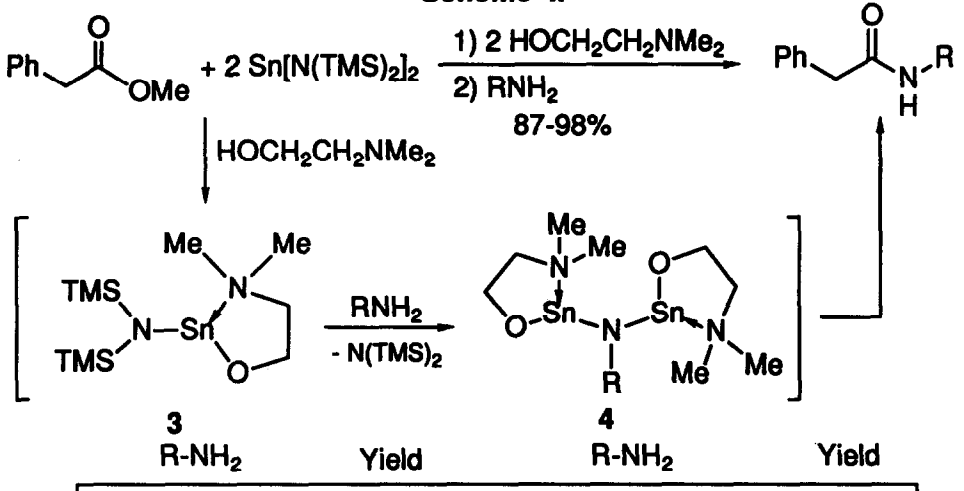
R-NH_2	Yield	R-NH_2	Yield
1-Phenylethylamine	98%	2-Methoxyethylamine	96%
4-Methoxyaniline	92%	*tert*-Butylamine	83%
Benzylamine	91%		

Although this substrate based approach to minimizing tin(II) amino cubane formation was successful, we realized that it would not always be practical or desirable to prepare a glycol ester in the course of a synthesis. Thus, we sought to develop a modified tin reagent that could be used effectively with a wide variety of esters.[7] One strategy to do this was to alter the nature of the nontransferable ligand in the tin reagent from silazane to a group such as t-butoxy. In fact, addition of 1 eq of t-butanol to $Sn[N(TMS)_2]_2$ followed by benzylamine and then methyl phenylacetate gave the amide in 47% yield instead of 22%. We obtained even better results, however, when we used the coordinating ligand, TMEDA, in conjunction with $Sn[N(TMS)_2]_2$.

When one equivalent of TMEDA was added to $Sn[N(TMS)_2]_2$ prior to addition of benzylamine and ester, we obtained the amide in 76% yield.

We were able to combine the effects of a coordinating ligand and an alkoxide when we incorporated N,N-dimethylethanolamine as the nontransferable ligand in our tin reagent. Under these conditions, a simple methyl ester can be transformed to a secondary amide in excellent yield! Using methyl phenylacetate as a standard substrate and N,N-dimethylethanolamine as the ancillary ligand on tin, we obtained N-benzyl, N-*t*-butyl, N-1-phenylethyl, and N-2-methoxyethyl amides in 87-98% yield (Scheme II). In the first step of this reaction, addition of N,N-dimethylethanolamine to $Sn[N(TMS)_2]_2$ gives tin(II) alkoxy amide **3** via exchange of one of the silazane ligands. Further reaction of this intermediate with the primary amine is thought to give a second tin(II) alkoxy amide **4**, which then converts the ester to an amide. The dramatic improvement in yield when N,N-dimethylethanolamine is used as the ancillary ligand can be ascribed to coordination of the pendant amino group to tin, thereby slowing further aggregation. Since this ligand is electron donating, it may also promote the transfer of the second amino group to the ester.

Scheme II



$R\text{-}NH_2$	Yield	$R\text{-}NH_2$	Yield
1-Phenylethylamine	97%	2-Methoxyethylamine	98%
4-Methoxyaniline	92%	*tert*-Butylamine	87%
Benzylamine	93%		

In conclusion, the modest yields obtained for the conversion of esters to secondary amides in our preliminary studies have been ascribed to the formation of unreactive tin(II) amino cubanes. In order to circumvent formation of these intermediates, we have developed two separate procedures, one of which is substrate based, the other, reagent based. Our substrate based strategy utilizes glycol esters to deliver the desired amino group via an intermediate

tin(II) alkoxy amide. In the reagent based approach, a tin(II) alkoxy amide is prepared *in situ* from $Sn[N(TMS)_2]_2$ and N,N-dimethylethanolamine. The following procedures are representative:

Glycol ester approach

A solution of 2-hydroxyethyl 2-phenylacetate (0.180 g, 1.00 mmol) in THF (3 mL) was added to a solution of $Sn[N(TMS)_2]_2$ (0.535 g, 1.20 mmol) in hexane (3 mL) at rt. After 5 min, a solution of benzylamine (0.128 g, 1.20 mmol) in THF (2 mL) was added and then the reaction was allowed to stir overnight. The reaction mixture was diluted with ethyl ether (100 mL) and washed with 15% aq KOH (2 x 10 mL), 20% aq KF (10 mL), and brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure to give 0.205 g (91%) of a N-benzyl 2-phenyacetate as a white solid: mp = 119-120°C, (lit. mp = 119-121°C);[8] ^1H NMR($CDCl_3$) δ 7.4-7.2 (m, 10H), 5.7 (bs, 1H), 4.4 (d, 2H, J = 5.8 Hz), 3.6 (s, 2H).

N,N-Dimethylethanolamine modified reagent approach

To a solution of $Sn[N(TMS)_2]_2$ (0.535 g, 1.20 mmol) and methyl phenylacetate (0.075 g, 0.50 mmol) in hexane (2 mL) at rt was added N,N-dimethylethanolamine (0.107 g, 1.20 mmol). After 5 min, the reaction mixture was treated with a solution of benzylamine (0.128 g, 1.20 mmol) in THF (2 mL), and then allowed to stir overnight. The reaction mixture was worked up as above to give 0.105 g (93%) of N-benzyl 2-phenyacetate.

Acknowledgement: We wish to thank the National Institutes of Health (GM42732) for partial support of this research, and C.A. Roskamp for helpful discussions.

REFERENCES & NOTES

1. Burnell-Curty, C.; Roskamp, E. J. *Synlett.* **1993**, *No. 2*, 131. Ibid. *J. Org. Chem.* **1992**, *57*, 5063.
2. Wang, W.-B.; Roskamp, E. J. *J. Org. Chem.* **1992**, *57*, 6101.
3. As a control study, benzylamine was allowed to react with methyl phenylacetate at rt in the absence of $Sn[N(TMS)_2]_2$. The desired N-benzyl amide was obtained in only 8% yield after a reaction time of 4 days.
4. When benzylamine and $Sn[N(TMS)_2]_2$ were allowed to react for 12 h before addition of methyl phenylacetate, no reaction with the ester was observed after 1 day.
5. Tin(II) amino cubanes have been prepared via reaction of $Sn[N(TMS)_2]_2$ with both benzylamine and t-butylamine. See, Veith, M. *Chem. Rev.* **1992**, *92*, 1, and references therein.
6. Tetrahydrofuran and hexane were found to be comparable solvents for this transformation. Reaction yields were modestly improved when a 1:1 mixture of THF and hexane was used.
7. We have been able to modify tin(II) reagents to dramatically improve the yields of other transformations, such as the cyclization of hindered β-amino esters to β-lactams. See, Wang, W.-B.; Roskamp, E. J. *J. Am. Chem. Soc.* **1993**, in press.
8. Sanguigni, J. A.; Levine, R. *J. Med. Chem.* **1964**, *7*, 573.

(Received in USA 6 August 1993; accepted 8 September 1993)